Recommendations Presented at the CIRM Conference, Stem Cell Research: Charting new Directions for California 2005

The first scientific meeting of the CIRM held in San Francisco on October 1 and 2, 2005, aimed to identify current challenges in the stem cell field and priorities for future research through presentations from leading stem cell researchers and the participation of scientists in the audience, patient advocates, and public attendees. The conference offered six scientific sessions, each focused on a topic of particular relevance to stem cell research. During the conference, the chairs and speakers from each session were asked to consider the possible challenges, opportunities, and future directions for stem cell research as they pertain to the theme of their specific session. At the final stage of the conference, each of the session chairs presented their group's recommendations to the CIRM. A summary of these recommendations, which were drafted from the session chairs' notes or slides, is presented below. A streaming video presentation of this material by the session chairs is available at The Science Network (www.csntv.org). An executive summary of the meeting will also be posted once it is finalized.

Session I: Cellular Therapeutics - Clinical State of the Art and Challenges for the Future

Settings Priorities

How will CIRM decide which diseases represent "low hanging fruit" and which are disease targets for the future?

Strategic planning groups for:

- Scientific and clinical analysis of current state of the art (expert working groups; Council at the National Institutes of Health)
- Define strengths inside/outside California (clinical excellence; scientific excellence)
- Create Requests for Proposals
- Provide continuous assessment as programs mature

Ways that CIRM can have an immediate, near term impact on stem cell based treatments:

- Highly purified human stem cells (HSCs) for treating genetic bone marrow disorders, autoimmune disease
  - Biology ready for translation
  - Trials are costly
  - Need methods for cell separation/isolation
- Translational/Integrative Research Network
  - Not solely Clinical Trial Network; more integrative research and development teams
  - Initially done for HSCs, but sets the stage for future studies (will evolve into Centers for clinical trial coordination of human embryonic stem cell (hESC)-based therapies)

Scientific Hurdles

- 1) Immunologic Barriers to Cell Transplant Strategies:
  - Generation of isogenic tissues
    Somatic cell nuclear transfer (SCNT); reprogramming
  - Tolerance induction
    Purified HSCs, re-education
- 2) Stem cell expansion or production (HSCs, etc); directed differentiation
  - For HSCs, expansion will facilitate Cord Blood applications
  - Bioprocess scale-up a common challenge to enable investigator initiated Phase I/II trials
  - Creation of defined cell types for transplant
- 3) Biology of cell repopulation
  - How do specific cell types integrate in situ?
  - Delivery mechanisms
  - Monoclonal antibody markers (reagents for cell isolation and clinical monitoring)

- Predictive animal models
- Imaging
- Standards to be established for pre-clinical proof-of-principle prior to trials

Facilities Needs

- Good Manufacturing Practices (GMP) facilities pre-exist
  - UCSF, Stanford, City of Hope, etc
  - Need to evaluate current capacity and project future needs
  - Do we need to invest now, or later?
- …but management is costly
  - Data management; research staff; regulatory; reagents
  - Need adequate funding to allow investigator initiated phase I/II trials
  - Needs to be positioned in the mid-term to support "non-Presidential" stem cell work (rather than CIRM funding completely independent laboratories, CIRM funds indirect cost reimbursements to allow "non-Presidential" work to go on in a facility that also has Federal Support)
- Animal cores
  - Large animal facility

Session II: Stem Cells and Therapies - Lessons from the FDA and Industry

Key Challenges

- Educating and empowering academics to move into clinical applications of stem cells
- Enabling access to sufficient number of cells made under GMP conditions
- Better imaging technologies required for better pre-clinical and clinical studies
- Scaling up to commercial scale production
- Better preservation techniques
- Supplies of appropriate growth factors

Recommendations

- To facilitate the empowerment of academics
  - Create series of workshops on GMP and regulatory issues
  - Facilitate industry collaborations by creating a directory of all companies and individuals capable of providing guidance
  - Create a state-wide consulting service

- Fund 2 or 3 regional centers for GMP production which are flexible and modular and which include quality control, quality assurance, storage and distribution capabilities

- Fund collaborations between basic scientists and groups experienced in scale-up to develop robust systems cell production at commercial scale.

Session III: Stem Cells as Tools for Disease Research and Therapy

Goal: Facilitate the translation of emerging technologies to clinical applications of human embryonic stem cells

Challenges

- Cells

  It is critical to develop technologies to define the molecular behavior of the stem cells in order use them effectively and reliably.

  Some Key Issues are:

  - Understand reprogramming to efficiently conduct SCNT
  - Use existing and newly created human embryonic stem cells to study the molecular basis of disease
  - Customize human embryonic stem cells and derivatives for clinical use
- Vectors
  - Develop safer genetic vectors to introduce genetic alteration in human embryonic stem cells as tools to develop therapies
  - Generate genetic vectors for high throughput discovery
- Chemicals
  - Design effective assays to apply toward key questions of self-renewal, differentiation, drug discovery

What is needed to meet these challenges?

- Centralized facilities
  - A human embryonic stem cell line bank is needed to house and distribute existing and newly generated, well-characterized human embryonic stem cell lines, including disease-specific lines
  - A vector core is needed to develop and generate genetic vectors that can be distributed broadly for research
  - A multi-purpose high throughput screening facility is needed to accelerate progress in basic stem cell research and drug discovery using:
    - small molecules
    - proteins
    - genes
- Support for investigator initiated basic research

Recommendations

- <u>Overall: Support Unfunded, Underfunded Research</u>
  - The CIRM should support research that is not funded, under-funded and mis-funded by NIH
  - The CIRM should focus on innovative research (mouse models, "fishing expeditions")
  - The CIRM should fund only research of the highest quality

- Short term
    - CIRM should coordinate the generation of reliable and well characterized human embryonic stem cell lines that can be distributed globally for human disease research
    - CIRM should invest in basic research to define molecular basis for "stemness" and stem cell behavior

- Intermediate term:

  Develop technologies for drug discovery and development
    - Invest in research to develop a safe/efficient method for homologous recombination
    - Develop reliable biomarker imaging for human embryonic stem cells and progeny
    - Develop effective cell assays to promote modeling efficiency and for high throughput screening purposes

- Long term:

  CIRM should establish central facilities
    - At least 2 (1 may be associated with GMP facility with training program)
    - **The structure and operation of these facilities needs careful examination

Session IV: Self-Renewal of Stem Cells

Scientific Goals

- Elucidate the self renewal mechanism of embryonic stem (ES) cells
- Develop culture conditions to optimize scale-up, to minimise or eliminate the use of animal products while optimising self renewal and genetic stability
- Achieve genetic manipulation of human stem cell self renewal

Key Challenges

- Lack of effective assays for pluripotency
- Systematic evaluation of the roles of stem cells in different tissues
- In those tissues that are stem cell maintained or repaired, definitively identify the stem cells and their corresponding niche cells at the single cell level.
- Scaling up ES cells -the loss of totipotency, homogeneity, and genetic stability during the process

Needs to Meet Key Challenges

- Translate the techniques for genetic manipulation of mouse ES cells to hESCs.
- Collaboration with biomedical engineers and cell and developmental biologists to address the challenges. Introduce multidisciplinary research methods to the identification of stem cells.
- Provision of reagents (growth factors, cell lines, antibodies, cell culture) to minimize costs and provide uniform quality control

Prioritized recommendations to CIRM and timelines

- Support efforts to reversibly block differentiation (3-5 years)
- Create multidisciplinary teams to identify conditions for stem cell maintenance and scaling-up. (2-4 years)
- Optimize transgenic method for hESCs. (1 year)
    - Optimize gene knock-out/knock-in methods. (3 years)
    - Develop controllable expression of key pluripotent regulatory genes. (4-5 years)

Session V: Fate Decisions - Good and Bad Choices

Top Three Challenges

- Improve our basic understanding of embryonic stem cells, normal and neoplastic tissue stem cells, their self renewal and differentiation control. This includes culture technologies and associated technical advances to enable further studies, like improvement in homologous recombination and others.

- Improve in vitro and in vivo complex functional analysis of stem cell properties and differentiation potential. This includes improvements in animal models to assess function and potential for tumorigenicity.

- Provide an extensive panel of research tools to accelerate all aspects of normal and neoplastic stem cell identification, isolation, and utility. This would include monoclonal antibodies, reporter lines, imaging tools, cytogenetic analysis, comparative genomic hybridization, DNA microarrays, and new separation tools.

Top Four Recommendations

- Primary method to meet this challenge is investigator-initiated grants of an individual, program, or even inter-institutional nature, judged primarily on the ability of the investigators to accomplish the work and its novelty. Special need to include younger researchers that may not have developed expertise in this area. Embryonic stem cells and essential reagents must be freely distributed.

- Core support for immune-deficient mouse models on-site or off-site linked to grant activity. Support for research to improve animal models for testing normal and neoplastic stem cells.

- Embryonic stem cell analysis core to enable uniform comparison of lines as a contract service.

- Embryonic stem cell line bank with HLA diversity via IVF, SCNT, and pre-implantation genetic diagnosis (PGD).

Session VI: Bridging the Gap between Bench and Bedside

Top Recommendations

- Studies on Lineage Commitment and Maturation of Target Populations with the goal of generating high purity populations of defined phenotypes (achievable over long term)
    - Tools such as genetic and cell surface markers, monoclonal antibodies
    - In vitro and in vivo clonogenic assays

- Support regulatory Quality Assurance guidance for translational stem cell projects that CIRM deems ripe for preclinical trials (achievable over short term)

- Support the profiling of human stem cells for pathogens and adverse genetic events (achievable over medium term) such as:
    - Tumorigenic studies
    - Cellular stability
    - Retroviral testing

- Optimization Studies for Translational Research (achievable over long term)
    - Clinically compliant culture conditions for propagation
    - Dosing studies for efficacy
    - Scale-up

- Rejection Prevention (achievable over long term)